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(54) Title: SUSTAINED RELEASE SALTS OF PHARMACEUTICALLY ACTIVE PEPTIDES AND THEIR PRODUCTION

(57) Abstract

Substained delivery pharmaceutical compositions comprise a water insoluble salt of a pharmaceutically active ionic peptide and a counterionic carrier macromolecule. The peptide may be an LHRH antagonist such as cetrorelix and the macromolecule may be an anionic polysaccharide such as carboxymethylcellulose. The salt is prepared using ion exchangers to sepArately remove the counterions from the peptide and the carrier macromolecule thereby forming free peptide/macromolecule ions. These free peptide and macromolecule ions are then combined to form the water insoluble peptide-macromolecule salt.

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SUSTAINED RELEASE SALTS OF PHARMACEUTICALLY ACTIVE PEPTIDES AND THEIR PRODUCTION

Background of the Invention

Field of Invention

This invention relates to pharmaceutical compositions of pharmacologically-active polypeptides, which provide sustained release of the polypeptide over an extended period of time.

Description of the Prior Art

According to the prior art (WO 98/25642) pharmaceutical formulations are claimed comprising a stable water-insoluble complex composed of a peptidic compound (e.g., a peptide, polypeptide, protein, peptidomimetic and the like), preferably a pharmaceutically active peptidic compound, and a carrier macromolecule that allow for sustained delivery of the peptidic compound in vivo upon administration of the complex. The complex according to the prior art can permit continuous delivery of a pharmaceutically active peptidic compound to a subject for prolonged periods of time, e.g., one month. Moreover, the association of the peptidic compound and the carrier macromolecule in a tight, stable complex allows for loading of high concentrations of the peptidic compound into the formulation.

The complex of the invention according to the prior art is formed by combining the peptidic compound and the carrier macromolecule under conditions such that a substantially water-insoluble complex is formed, e.g, aqueous solutions of the peptidic compound and carrier macromolecule are mixed until the complex precipitates.

The complex may be in the form of a solid (e.g., a paste, granules, a powder or a lyophilizate) or the powdered form of the complex can be pulverized finely enough to form stable liquid suspensions or semi-solid dispersions.

In a preferred embodiment, the peptidic compound of the water-insoluble complex is an LHRH analogue, more preferably an LHRH antagonist, and the carrier macromolecule is an anionic polymer, preferably sodium carboxymethylcellulose. The complex of the invention is suitable for sterilization, such as by gamma irradiation or electron beam irradiation, prior to administration in vivo. Methods for treating a subject for a condition treatable with an LHRH analogue by administering to the subject an LHRH-analogue-containing composition of the invention are also provided.

Problems presented by the Prior Art

For manufacturing the claimed complexes rather highly concentrated solutions (5 - 25 mg/ml) of the peptidic compound in water have to be prepared. Because of the inherent tendency of many peptidic compounds to aggregate, it can not be ensured that aggregate-free solutions in pure water can be prepared using the claimed manufacturing procedure. Depending on the water solubility of a specific peptidic compound and on the technique used to prepare this solution, the concentrated peptide solution in water may be aggregate-free or contaminated with varying concentrations and different types of peptidic aggregates and precipitates. As this highly concentrated peptidic solution is the starting material for the production of the claimed complexes, the dissolution of the peptidic compound in water is obviously a critical step.

By adding an aqueous solution of sodium carboxymethylcellulose to this not well defined and characterized, highly concentrated petide solutions in varying ratios (0,1:1 to 0,5: 1 w/w) complexes or precipitates are formed spontaneously in a non-defined, uncontrolled manner. The precipitates are collected by filtration or centrifugation, washed by rinsing with water and dried. The solid material is then powdered using a mortar and pestle. Afterwards the content of the peptidic compound is analytically determined. Due to the manufacturing procedure, the formation of stoichiometric complexes in a reproducible and well defined manner can not be guaranteed.

Additionally, by adding a solution of sodium carboxymethylcellulose (containing 6,5-9,5 % sodium according to USP) a significant amount of metall ions, i.e. sodium ions, comes into contact with the peptidic compound. Peptides and proteins might be precipitated in the presence of salts. Therefore, it is not clear, whether the complexes or precipitates described in the prior art are formed because of interactions between the peptidic compound and the functional groups of carboxymethylcellulose itsself or solely by the peptide precipitating effect of the sodium ions or by unknown and non-controllable mixtures of these two processes.

After drying and milling the peptide formulations described in the prior art are suspended in saline, which also can lead to further undesirable, uncontrolled interaction processes.

Summary of the Invention

The present invention provides pharmaceutical compositions comprising a stable, well defined, stoichiometric salt composed of an acidic or basic peptidic compound (like peptide, polypeptide protein, peptidominetic etc.) and of an ionic, basic or acidic, carrier macromolecule, respectively, allowing sustained delivery of the peptidic compound after in vivo administration of the salt of a specific peptidic compound.

The ionic carrier macromolecule may be an anionic polymer, for example an anionic polyalcohol, a derivative or a fragment thereof.

Furthermore the ionic carrier macromolecule can be an anionic polysaccharide, a derivative or a fragment thereof. Preferably the carrier macromolecule is carboxymethylcellulose.The carrier macromolecule in the pharmaceutical composition can further be selected from the group consisting of algin, alginic acid, sodium alginate, anionic acetate polymers, ionic acrylic or methacrylic polymers and copolymers, pectin, tragacanth, xanthan gums, anionic carageenan derivatives,

anionic polygalacturonic acid derivatives, sulfated and sulfonated polystyrene, sodium starch glycolate, and fragments or derivatives thereof.

The ionic carrier macromolecule can also be albumin, gelatin (type A or type B), and a fragment or derivative thereof.

Cationic polymers can also be poly-L-lysine and other polymers of basic amino acids.

The peptide in the compound is a pharmaceutically active peptidic compound and can be a mono-, di- or multivalent cationic or anionic polypeptide, wherein the polypeptide is 5 to 100 amino acids in length, preferabely 5 to 20 amino acids in length, more preferabely the peptide is 8 to 12 amino acids in length. More in detail the peptidic compound is an LHRH analogue and the LHRH analogue is an LHRH antagonist. The LHRH analogue is for example Cetrorelix, Teverelix (Antarelix, Deghenghi et al., Biomed & Pharmacother 1993, 47, 107), Abarelix (Molineaux et al., Molecular Urology 1998, 2, 265), Ganirelix (Nestor et al., J. Med. Chem. 1992, 35,3942), Azaline B, Antide, A-75998 (Cannon et al., J. Pharm. Sci. 1995, 84, 953), Detirelix (Andreyko et al., J. Clin. Endocrinol. Metab. 1992, 74, 399), RS-68439 , Ramorelix (Stoeckemann and Sandow, J. Cancer Res. Clin. Oncol. 1993, 119, 457), Nal-Glu. Structures of the above mentioned LHRH analogues are provided for example in the above cited references and in following reviews: Behre et al., GnRH antagonists: an overview, Proceedings of the 2nd World Conference on Ovulation Induction, The Parthenon Publishing Group Ltd, UK; Kutscher et al., Angew. Chem. 1997, 109, 2240.

Moreover a method of preparation of such salts is described.

According to the invention, the free base or the free acid of the peptidic compound is prepared by removing the counter ion using ion exchangers. Also, the free base or the free acid of the carrier macromolecule is prepared by removing the counter ion using ion exchangers. Thereupon, equivalent amounts of the freshly prepared peptide base or peptide acid solution, respectively, and of the counterionic-free macromolecule carrier solution are combined. The ratio of peptidic compound to

carrier macromolecule (w/w) can be, for example, 1:0.1, 1:0.213, 1:0.5, 1:2.13. Non-limiting examples of conditions and procedures for preparing a water-insoluble complex of the invention are described in Examples 1 to 4.

This process results in well defined, stoichiometric and pure salts of the peptidic compound with a counterionic macromolecule. These pure salts are not contaminated by other ions, neither anions (e.g. acetate) nor cations (e.g. sodium).

The pharmaceutical compositions of the invention permit sustained delivery of the peptidic compound to a subject in vivo after administration of the composition to the subject. The duration and the extent of the sustained delivery can be varied depending upon the concentration of the peptidic compound and the carrier macromolecule used to form the salt.

Example 1

A lyophilisate of cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.1 resembling a molar ratio cetrorelix : carboxylic function of CMC of 1:0.48 was prepared as follows. 0.22 g Na-CMC (low viscosity grade carboxymethylcellulose, Hercules) was dissolved in 40 g water and 3 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. 2.21 g cetrorelix acetate was dissolved in 23.4 g water and 74.6 g ethanol 96 % (v/v) was added. 20 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. The filtrated cetrorelix base solution was added under continuous stirring to the sodium-free CMC-solution yielding a clear solution. After 1 hour stirring the solution was evaporated under vacuum to remove the ethanol yielding a dispersion. Finally, the dispersion was frozen and freeze-dried.

Example 2

A lyophilisate of cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.213 resembling a molar ratio cetrorelix : carboxylic function of CMC of 1:1 was prepared as follows. 0.426 g Na-CMC (low viscosity grade carboxymethylcellulose, Hercules) was dissolved in 40 g water and 5 g ion exchanger (Amberlite®) was added. After stirring for 25 min the ion exchanger was removed by filtration using a glas fibre filter. 2.21 g cetrorelix acetate was dissolved in 23.4 g water and 74.6 g ethanol 96 % (v/v) was added. 20 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. The filtrated cetrorelix base solution was added under continuous stirring to the sodium-free CMC-solution yielding a clear solution. After 1 hour stirring the solution was evaporated under vacuum to remove the ethanol yielding a dispersion. Finally, the dispersion was frozen and freeze-dried.

Example 3

A lyophilisate of cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.5 resembling a molar ratio cetrorelix : carboxylic function of CMC of 1:2.41 was prepared as follows. 1.1 g Na-CMC (low viscosity grade carboxymethylcellulose, Hercules) was dissolved in 200 g water and 15 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. 2.21 g cetrorelix acetate was dissolved in 23.4 g water and 74.6 g ethanol 96 % (v/v) was added. 20 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. The filtrated cetrorelix base solution was added under continuous stirring to the sodium-free CMC-solution yielding a solution. After 1 hour stirring the solution was evaporated under vacuum to remove the ethanol yielding a dispersion. Finally, the dispersion was frozen and freeze-dried.

Example 4

A lyophilisate of cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:2.13 resembling a molar ratio cetrorelix : carboxylic function of CMC of 1:10 was prepared as follows. 4.26 g Na-CMC (low viscosity grade carboxymethylcellulose, Hercules) was dissolved in 400 g water and 50 g ion exchanger (Amberlite®) was added. After stirring for 25 min the ion exchanger was removed by filtration using a glas fibre filter. 2.21 g cetrorelix acetate was dissolved in 23.4 g water and 74.6 g ethanol 96 % (v/v) was added. 20 g ion exchanger (Amberlite®) was added. After stirring for 20 min the ion exchanger was removed by filtration using a glas fibre filter. The filtrated cetrorelix base solution was added under continuous stirring to the sodium-free CMC-solution yielding a turbid dispersion. After 1 hour stirring the dispersion was evaporated under vacuum to remove the ethanol. Finally, the dispersion was frozen and freeze-dried.

Example 5

The solubility of sodium-free, pure CMC-salts with varying compositions peptide-base : CMC acid was determined in isotonic Ringer solution. The cetrorelix-CMC-salts were prepared according to example 1 to 4. Additionally, the in vitro release in Ringer solution of cetrorelix out of these sodium-free CMC-salts was tested over a time period of 168 hours using a flow-through-system. The amount of cetrorelix released after 168 h is expressed as percentage of the cetrorelix dose applied in this in vitro test method.

peptide-base:CMC (w/w)	solubility in Ringer solution in µg/ml	in vitro release in Ringer solution after 168 h in %
1:0,1	3,5	23
1:0,213	2,7	30
1:0,5	17,5	63
1:2,13	54	76

These in vitro data of the sodium-free CMC-salts according to this invention were compared with cetrorelix complexes manufactured with Na-CMC in identical mass ratios of peptide and CMC according to the prior art (WO 98/25642).

peptide-base:Na-CMC (m/m)	solubility in Ringer solution in µg/ml	in vitro release in Ringer solution after 168 h in %
1:0,1	2,5	46
1:0,253	1,5	48
1:0,5	2	45
1:2,13	2	17

The elimination of sodium and acetate ions in the peptide CMC-salts is leading to significant improvements in the in vitro bevaviour of such formulations, i.e. solubility and in vitro release characteristics.

In the Na-CMC complexes according to the prior art the solubility in Ringer solution is very low and can not be modified by changing the ratio of the components peptide and Na-CMC. Thus, the release kinetics of the peptidic compound out of these formulations cannot be modified.
In contrast, within the sodium-free CMC-salts of the peptidic compound prepared according to the invention there is a clear dependence between the mass ratio of the salt components and their in vitro behaviour. An increase in the percentage of sodium-free CMC acid within such formulations leads to a significant increase in the solubility of the peptidic compound in Ringer solution. Thus, the release kinetics of the peptidic compound out of these sodium-free CMC-salt formulations can be modified and controlled. Therefore, depending on the desired release kinetics for certain clinical applications, definite CMC-salt formulations with appropiate release patterns can be made available.

Example 6

Both sodium-free CMC-salts of cetrorelix according to Examples 1 to 4 and Na-CMC-complexes of cetrorelix with equivalent mass ratios cetrorelix : CMC according to the prior art were prepared. Suspensions of such sodium-free CMC-salts of cetrorelix

and of Na-CMC-complexes of cetrorelix, respectively, were prepared and a single dose was injected intramuscularly into rats in a dosage of 1,5 mg/kg. Plasma testosterone levels and plasma cetrorelix levels were determined at various time points. Additionally, at the end of the testosterone suppression the rats were killed. The muscle, into which the dose was injected, was removed and analyzed for the residual of the administered cetrorelix dose at the injection site.

Results are shown in Figure 1.

The absolute bioavailability of the Cetrorelix-CMC salts was in the range of 78%-111%. The bioavailability of the Cetrorelix-Na-CMC complexes was only 32% indicating the negative influence of the sodium ions on the properties of the formulations prepared according to the prior art.

Example 7

Sodium-free CMC-salts of cetrorelix according to this invention as described in previous examples were prepared as lyophilisates. The lyophilisates were dispersed in aqueous media and a single dose was injected subcutaneously into dogs in a dosage of 1,0 mg/kg. Plasma testosterone levels and plasma cetrorelix levels were determined at various time points. Results are shown in Figure 2.

Claims

1. A pharmaceutical composition comprising a water-insoluble salt of a pharmaceutically active ionic peptidic compound and a counterionic carrier macromolecule.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutically active peptidic compound is cationic and the carrier macromolecule is anionic.

3. The pharmaceutical composition of claim 1, wherein the pharmaceutically active peptidic compound is anionic and the carrier macromolecule is cationic.

4. The pharmaceutical composition of claim 1, wherein the formation of the water-insoluble salt can be mediated additionally at least in part by hydrogen bonding between the pharmaceutically active peptidic compound and the carrier macromolecule.

5. The pharmaceutical composition of claim 1, wherein the formation of the water-insoluble salt can be mediated additionally at least in part by hydrophobic interactions between the pharmaceutically active peptidic compound and the carrier macromolecule.

6. The pharmaceutical composition of claim 1, wherein a single dose of the water-insoluble salt provides sustained delivery of the pharmaceutically active peptide to a subject for at least one week after the pharmaceutical composition is administratered to the subject.

7. The pharmaceutical composition of claim 1, wherein a single dose of the water-insoluble salt provides sustained delivery of the pharmaceutically active peptide to a subject for at least two weeks after the pharmaceutical composition is administratered to the subject.

8. The pharmaceutical composition of claim 1, wherein a single dose of the water-insoluble salt provides sustained delivery of the pharmaceutically active peptide to a subject for at least three weeks after the pharmaceutical composition is administratered to the subject.

9. The pharmaceutical composition of claim 1, wherein a single dose of the water-insoluble salt provides sustained delivery of the pharmaceutically active peptide to a subject for at least four weeks after the pharmaceutical composition is administratered to the subject.

10. The pharmaceutical composition of claim 1, wherein the pharmaceutically active peptidic compound is a mono-, di- or multivalent cationic or anionic peptide.

11. The pharmaceutical composition of claim 1, wherein the peptidic compound is a mono-, di- or multivalent ampholytic peptide.

12. The pharmaceutical composition of claim 1, wherein the peptide is 5 to 100 amino acids in length.

13. The pharmaceutical composition of claim 1, wherein the peptide is 5 to 20 amino acids in length.

14. The pharmaceutical composition of claim 1, wherein the peptide is 8 to 12 amino acids in length.

15. The pharmaceutical composition of claim 1, wherein the carrier macromolecule is an anionic polymer.

16. The pharmaceutical composition of claim 1, wherein the carrier macromolecule is an ampholytic polymer.

17. The pharmaceutical composition of claim 1, wherein the carrier macromolecule is an anionic polyalcohol, a derivative or a fragment thereof.

18.The pharmaceutical composition of claim 1, wherein the carrier macromolecule is an anionic polysaccharide, a derivative or a fragment thereof, or a pharmaceutically acceptable salt thereof.

19.The pharmaceutical composition of claim 1, wherein the carrier macromolecule is carboxymethylcellulose.

20.The pharmaceutical composition of claim 1, wherein the carrier macromolecule is selected from the group consisting of algin, alginic acid, sodium alginate, anionic acetate polymers, ionic acrylic or methacrylic polymers and copolymers, pectin, tragacanth, xanthan gums, anionic carageenan derivatives, anionic polygalacturonic acid derivatives, sulfated and sulfonated polystyrene, sodium starch glycolate, and fragments or derivatives thereof, respectively.

21.The pharmaceutical composition of claim 1, wherein the ionic carrier macromolecule is selected from the group consisting of albumins, gelatin type A, gelatin type B, and fragments or derivatives thereof.

22.The pharmaceutical composition of claim 1, wherein the ionic carrier is a cationic macromolecule like poly-L-lysine and other polymers of basic amino acids

23.The pharmaceutical composition of claim 1, which is a dry solid.

24.The pharmaceutical composition of claim 1, which is a liquid suspension or semi-solid dispersion.

25.A pharmaceutical composition comprising a water-insoluble salt, wherein the water-isoluble salt consists essentially of a pharmaceutically active peptidic compound and a carrier macromolecule.

26.The pharmaceutical composition of claim 25 comprising a water-insoluble salt of an LHRH analogue and a carrier macromolecule.

27.The pharmaceutical composition of claim 26 comprising a water-insoluble salt of an LHRH antagonist and a carrier macromolecule.

28.The pharmaceutical composition of claim 25, wherein the peptide-CMC-salt has a mass ratio peptide : CMC ranging from 1:0.006 to 1:40, preferably from 1:0.04 to 1:14, more preferably from 1:0.1 to 1:5, especially from 1:0.1 to 1:3.

29.The pharmaceutical composition of claim 26, wherein the peptide-CMC-salt has a mass ratio peptide : CMC ranging from 1:0.006 to 1:40, preferably from 1:0.04 to 1:14, more preferably from 1:0.1 to 1:5, especially from 1:0.1 to 1:3.

30.The pharmaceutical composition of claim 27, wherein the peptide-CMC-salt has a mass ratio peptide : CMC ranging from 1:0.006 to 1:40, preferably from 1:0.04 to 1:14, more preferably from 1:0.1 to 1:5, especially from 1:0.1 to 1:3.

31.The pharmaceutical composition of claim 27, wherein the LHRH antagonist is cetrorelix.

32.The pharmaceutical composition of claim 30, wherein the peptide is cetrorelix.

33.The pharmaceutical composition of claim 30, wherein the peptide salt is a cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.1.

34.The pharmaceutical composition of claim 30, wherein the peptide salt is a cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.213.

35.The pharmaceutical composition of claim 30, wherein the peptide salt is a cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:0.5.

36.The pharmaceutical composition of claim 30, wherein the peptide salt is a cetrorelix-CMC-salt with a mass ratio cetrorelix : CMC of 1:2.13.

37.A method for preparing a pharmaceutical formulation, comprising a peptidic compound and a carrier macromolecule; forming the free ions of both compounds by removing the counter ions; combining the ionic peptidic compound and the ionic carrier macromolecule under conditions such that a water-insoluble salt of the peptidic compound and the carrier macromolecule forms; and preparing a pharmaceutical formulation comprising the water insoluble salt.

38.The method of claim 37 wherein a solution of the ionic peptidic compound and a solution of the carrier macromolecule are fresh prepared before combined to form a water-insoluble salt of the peptidic compound and the carrier macromolecule.

39.The method of claim 37 wherein a solution of the ionic peptidic compound and a solution of the carrier macromolecule are combined to form a water-insoluble salt of the peptidic compound and the carrier macromolecule.

40.The method of claim 37, further comprising sterilizing the water-insoluble salt by gamma irradiation or electron beam irradiation.

41.The method of claim 37, wherein the water-insoluble salt is formed using aseptic procedures.

42.The method of claim 37, wherein the peptidic compound is cationic and the carrier macromolecule is anionic.

43.The method of claim 37, wherein the peptidic compound is anionic and the carrier macromolecule is cationic.

44.The method of claim 37, wherein the peptidic compound is a mono-, di- or multivalent cationic or anionic peptide.

45.The method of claim 37, wherein the peptidic compound is a mono-, di- or multivalent ampholytic peptide.

46.The method of claim 37, wherein the peptidic compound is an LHRH analogue.

47.The method of claim 46, wherein the LHRH analogue is an LHRH antagonist.

48.The method of claim 47, wherein the LHRH antagonist is Cetrorelix.

49.The method of claim 47, wherein the LHRH antagonist is Teverelix.

50.The method of claim 47, wherein the LHRH antagonist is Abarelix.

51.The method of claim 47, wherein the LHRH antagonist is Ganirelix RS-26306.

52.The method of claim 47, wherein the LHRH antagonist is Azaline B.

53.The method of claim 47, wherein the LHRH antagonist is Antide ORF-23541.

54.The method of claim 47, wherein the LHRH antagonist is A-75998.

55.The method of claim 47, wherein the LHRH antagonist is Detirelix RS-68439.

56.The method of claim 47, wherein the LHRH antagonist is Ramorelix HOE-2013.

57.The method of claim 47, wherein the LHRH antagonist is Nal-Glu ORF-21234.

Figure 1 / Example 6

Cetrorelix plasma levels in rats following a single dose of 1.5 mg/kg in different Cetrorelix-CMC formulations

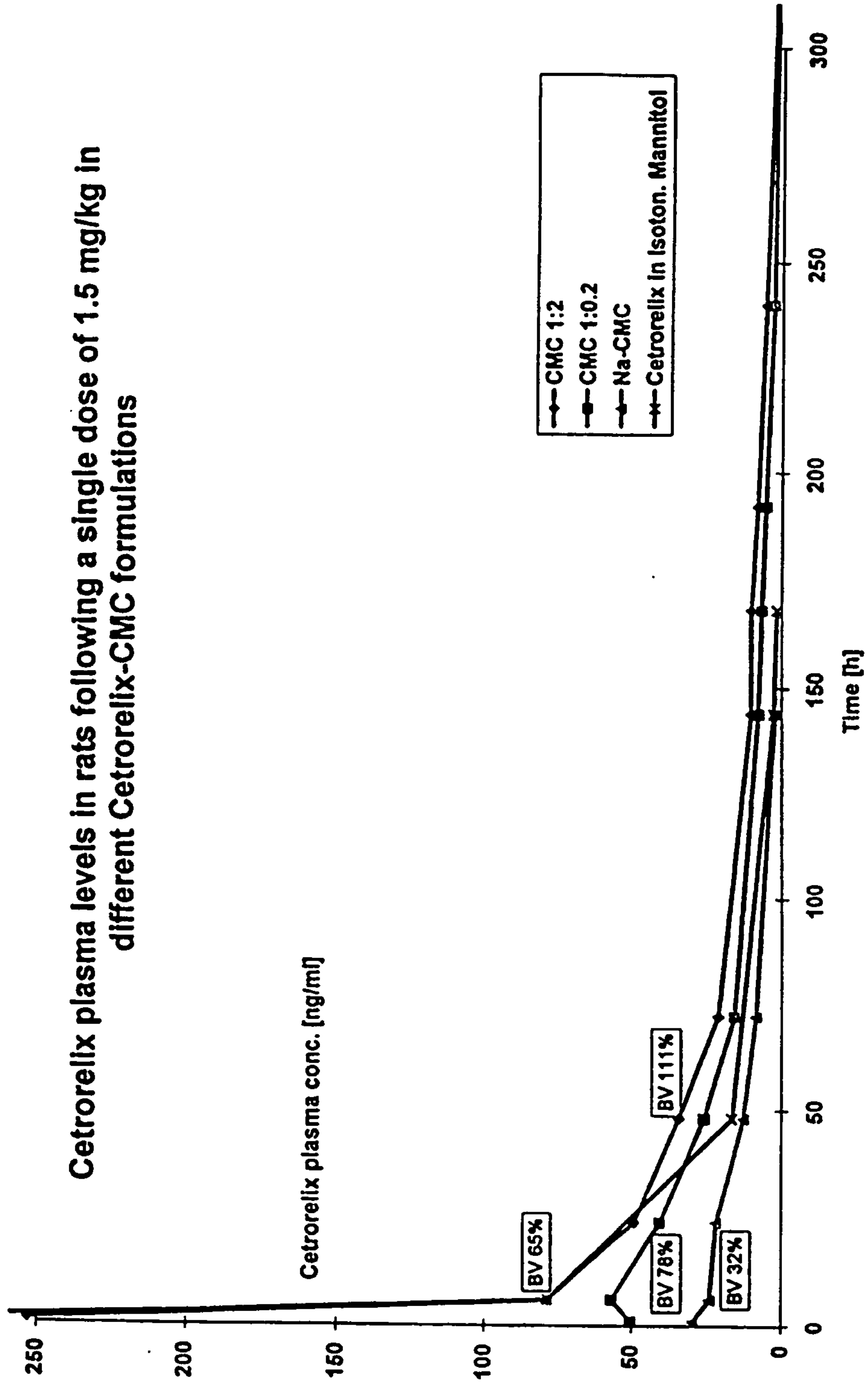
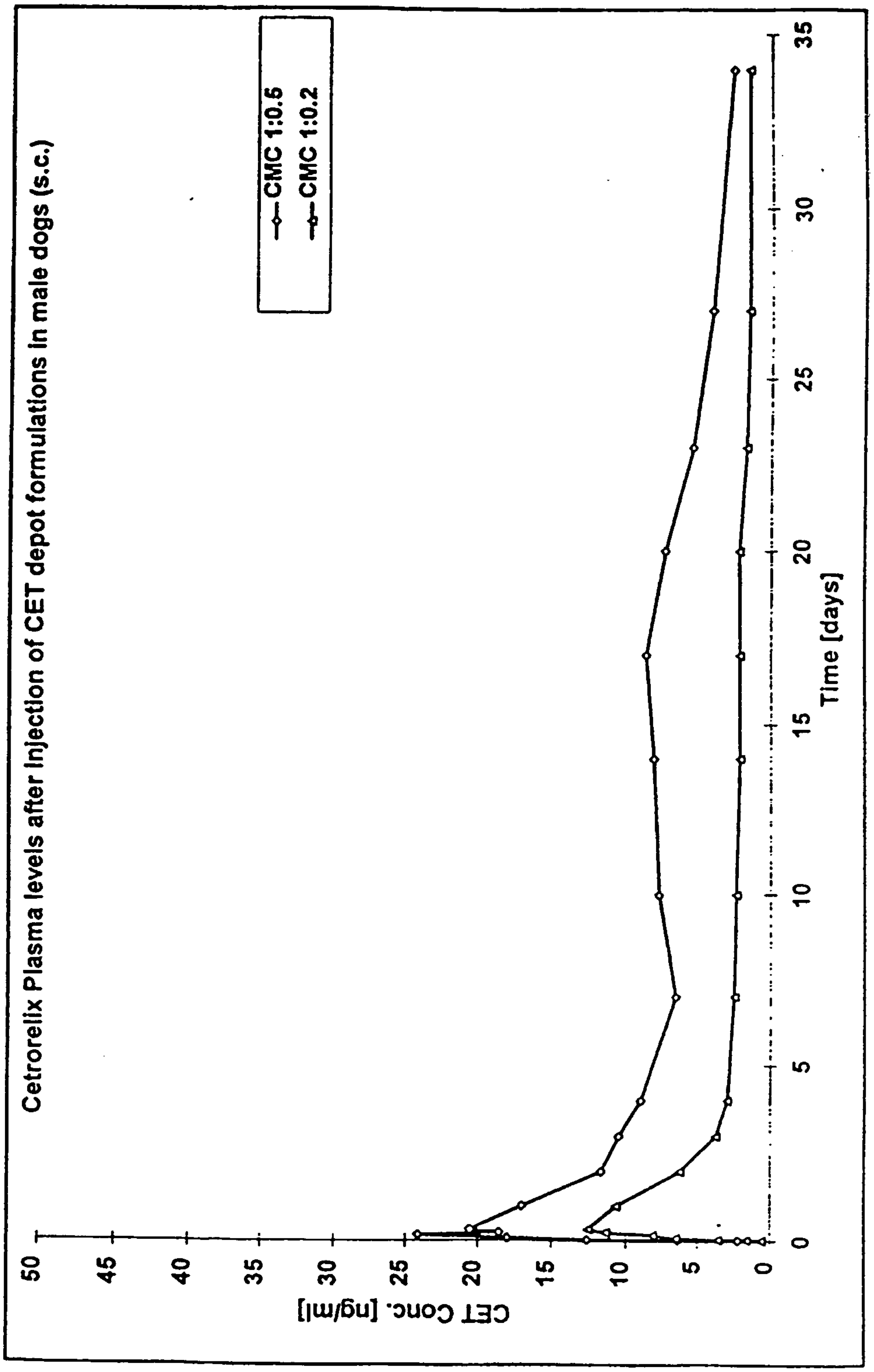


Figure 2 / Example 7



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/00697

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K38/09 A61K9/10 A61K9/14 A61K9/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 24150 A (ZENECA LTD) 9 December 1993 (1993-12-09) abstract examples 1-25	1-36
X	US 4 581 169 A (NESTOR JOHN J ET AL) 8 April 1986 (1986-04-08) column 2, line 28 - line 41 column 9, line 17 - line 29	1-36
X	WO 98 32423 A (KAMEI SHIGERU ;SAIKAWA AKIRA (JP); IGARI YASUTAKA (JP); OHTA TSUTO) 30 July 1998 (1998-07-30) page 14, line 18 - line 24 page 15, line 25 - line 34 page 38, line 34 -page 39, line 4 examples 1-15	1-24

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[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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